RESEARCH COMMUNICATION

NER and BER Repair Gene Polymorphisms in a Healthy North Indian Cohort and Comparison with Different Ethnic Groups Worldwide

Raju K Mandal, Tulika Mittal, Rakesh Kapoor, Rama Devi Mittal*

Abstract

**Background:** Polymorphisms in DNA repair genes are associated with ability to remove DNA lesions, and therefore may contribute to an individual's susceptibility to different types of cancer. Base excision repair (BER), and nucleotide excision repair (NER) are the main DNA repair pathways. The present study was conducted to determine the frequency distribution of single nucleotide polymorphisms (SNPs) selected for genes in these two pathways i.e. *OGG1* Exon 7 (C1245G), *XPC* Intron 9 (PAT), and Exon 15 (A33512C) in a North Indian population in comparison with global populations. **Methods:** Genotyping was achieved by PCR-based analysis in 224 normal healthy, unrelated individuals of similar ethnicity. **Results:** Allelic frequencies in wild type of *OGG1* Exon 7 C>G were 73% (C); *XPC* PAT D>I 75% (D); and *XPC* Exon 15 A>C 60.71.9% A. On the other hand, the variant allele frequency were 27% (G) in *OGG1* Exon 7 C>G; 25% (I) in *XPC* PAT; and 28.1% (C) in *XPC* Exon 15 A>C. Major differences from other ethnic populations were observed. **Conclusions:** Our results suggest that frequency distribution in these DNA repair genes exhibited a distinctive pattern in our population which could be attributed to ethnic variation. This could assist in high-risk screening of humans exposed to environmental carcinogens and cancer predisposition in different ethnic groups.

**Keywords:** DNA repair genes - polymorphisms - ethnic groups

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Introduction

Genetic variation in human genome is an emerging resource for studying cancer, a complex disease characterized by both environmental and genetic contributions. Gene-environment interactions may be manifested in various ways, either by risk effects based on an individual’s genotype, or differential gene risk effects based on exposure (Vispe et al.,2000).

DNA in most cells is regularly damaged by endogenous and exogenous mutagens. Unrepaired damage can result in apoptosis or may lead to unregulated cell growth and cancer. If DNA damage is recognized by cell machinery, several responses may occur to prevent replication in the presence of genetic errors. At the cellular level, checkpoints can be activated to arrest the cell cycle, transcription can be up-regulated to compensate for the damage, or the cell can apoptose. Alternatively, the damage can be repaired at the DNA level enabling the cell to replicate as planned.

NER and BER Repair Gene Polymorphisms in Healthy Indians in Comparison with Different Ethnic Groups Worldwide

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Genotypic analysis of the OGG1 Exon 7 polymorphism was conducted using the PCR-RFLP method. Five ml of blood was collected in EDTA vials and DNA was extracted from blood lymphocytes using the salt-out method (Miller et al., 1998). DNA was subsequently used for comparison with our study.

Prevalence of gene variants

We conducted a MEDLINE search using “OGG1”, “XPC”, “polymorphism” for papers published before December 2009. The search was limited to human subjects, without language restriction. For case-control studies, only genotype frequencies for the control population were included. Studies based on fewer than 90 persons were excluded. The most recent publication was included in the study when more than one article was identified for the same study population. We identified 9 publications reporting on the prevalence of OGG1 Exon 7 polymorphism, 4 publications on XPC PAT and 3 for XPC Exon 15 which were subsequently used for comparison with our study.

Statistical analysis

Pearson’s χ² test was done to compare the genotype and allelic frequencies of different populations using the software SPSS (version 11.5). Court-Lab (web-based software) was used to examine Hardy-Weinberg equilibrium (www.tufts.edu). P-value 0.05 was considered to be statistically significant.

Results

The distribution of OGG1 Exon 7, XPC PAT, and XPC Exon 15 genotypes and allele frequencies in northern Indian population are shown in Table 1. Genotype distributions and allelic frequencies in northern Indian population are shown in Table 1. Genotype distributions and allele frequencies in various populations using the software SPSS (version 11.5). Court-Lab (web-based software) was used to examine Hardy-Weinberg equilibrium (www.tufts.edu). P-value 0.05 was considered to be statistically significant.

Table 2. Genotypes and Allele Frequency Distribution of OGG1 Exon 7 Gene Polymorphism in Various Populations and P-value in Comparison to North Indian Population

<table>
<thead>
<tr>
<th>Gene</th>
<th>Country/ethnicity</th>
<th>n</th>
<th>Mean age ± SD</th>
<th>Genotype</th>
<th>Ref</th>
<th>P-value</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGG1 Exon 7</td>
<td>North India</td>
<td>224</td>
<td>59.1 ± 10.4</td>
<td>CC</td>
<td>Ref 27 Present Study</td>
<td>116 (51.8)</td>
<td>95 (42.4)</td>
</tr>
<tr>
<td>Japan</td>
<td>121</td>
<td>67.4 ± 6.7</td>
<td>39 (32.2)</td>
<td>54 (44.6)</td>
<td>28 (23.2)</td>
<td>0.033</td>
<td>18.9 Nock et al., 2006</td>
</tr>
<tr>
<td>Spain</td>
<td>323</td>
<td>-</td>
<td>210 (64.9)</td>
<td>104 (32.3)</td>
<td>9 (2.8)</td>
<td>&lt;0.001</td>
<td>34.6 Zienolddiny et al., 2006</td>
</tr>
<tr>
<td>Norway</td>
<td>386</td>
<td>60 (50-85)</td>
<td>194 (50.3)</td>
<td>117 (30.3)</td>
<td>75 (19.4)</td>
<td>&lt;0.001</td>
<td>34.6 Zienolddiny et al., 2006</td>
</tr>
<tr>
<td>Minnesota</td>
<td>599</td>
<td>59.7 ± 12.1</td>
<td>339 (57)</td>
<td>223 (37)</td>
<td>37 (6)</td>
<td>0.938</td>
<td>24.8 McWilliams et al., 2008</td>
</tr>
<tr>
<td>Korea</td>
<td>247</td>
<td>-</td>
<td>52 (21.1)</td>
<td>131 (53.0)</td>
<td>64 (25.9)</td>
<td>&lt;0.001</td>
<td>52.4 Kim et al., 2003</td>
</tr>
<tr>
<td>Turkey</td>
<td>250</td>
<td>53.19 ± 0.75</td>
<td>115 (46)</td>
<td>106 (42.4)</td>
<td>29 (11.6)</td>
<td>0.024</td>
<td>32.8 Karahalih et al., 2008</td>
</tr>
<tr>
<td>USA</td>
<td>479</td>
<td>62.8 ± 9.1</td>
<td>305 (63.8)</td>
<td>142 (29.7)</td>
<td>32 (6.5)</td>
<td>0.849</td>
<td>21.5 Nock et al., 2006</td>
</tr>
<tr>
<td>Poland</td>
<td>100</td>
<td>-</td>
<td>68 (68)</td>
<td>28 (28)</td>
<td>4 (4)</td>
<td>0.276</td>
<td>18 Sliwinski et al., 2009</td>
</tr>
</tbody>
</table>

Table 1. Genotypes and Allele Frequency Distribution of OGG1 Exon 7, XPC Pat And XPC Exon 15 Gene Polymorphism in North India

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Observed (n)</th>
<th>Expected (n)</th>
<th>Minor allele freq (HWE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGG1 Exon 7</td>
<td>CC</td>
<td>116 (51.8)</td>
<td>119 (53.3)</td>
<td>27</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>C1245G</td>
<td>95 (42.4)</td>
<td>89 (39.4)</td>
<td>14</td>
<td>0.25</td>
</tr>
<tr>
<td>(rs1052133)</td>
<td>GG</td>
<td>13 (5.8)</td>
<td>16 (7.3)</td>
<td>17</td>
<td>0.25</td>
</tr>
<tr>
<td>XPC Intron 9</td>
<td>D/D</td>
<td>124 (55.3)</td>
<td>126 (56.2)</td>
<td>25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>I/I</td>
<td>12 (5.4)</td>
<td>14 (6.3)</td>
<td>17</td>
<td>0.25</td>
</tr>
<tr>
<td>PAT</td>
<td>D/I</td>
<td>88 (39.3)</td>
<td>84 (37.5)</td>
<td>25</td>
<td>0.25</td>
</tr>
<tr>
<td>(AF076952)</td>
<td>I/I</td>
<td>12 (5.4)</td>
<td>14 (6.3)</td>
<td>17</td>
<td>0.25</td>
</tr>
<tr>
<td>XPC Exon 15</td>
<td>AA</td>
<td>114 (50.9)</td>
<td>116 (51.7)</td>
<td>28</td>
<td>0.25</td>
</tr>
<tr>
<td>(rs2228001)</td>
<td>AC</td>
<td>94 (42.0)</td>
<td>91 (40.4)</td>
<td>17</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>16 (7.1)</td>
<td>17 (7.9)</td>
<td>17</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Recent studies identified the XPC-HR23B complex as the first protein component that recognizes and binds to the damaged sites. An intronic biallelic polymorphism (AT insertion/deletion polymorphism (XPC PAT)) of the XPC gene consisting of an insertion of 83 bases of A and T [poly (AT)] and deletion of 5 bases (GTAAC) at positions 1457 to 1461 in intron 9 has been reported. XPC-PAT polymorphism has been reported to be in linkage disequilibrium with a single nucleotide polymorphism in XPC Exon 15 that causes an amino acid change Lys939Gln (A33512C, rs2228001) has also been reported. Interestingly, defects in XPC have been associated with many types of cancer (Wang et al., 2003). The present study is an attempt to investigate frequency distribution of OGG1, XPC genes polymorphism by using a PCR-based restriction analysis in unrelated normal healthy individuals from North India.

Materials and Methods

Subjects

The study involved 224 subjects from the North Indian population, which included unrelated healthy subjects from same geographical region. The hospital ethics committee approved the study and informed consent was obtained from the participating volunteers.

DNA Extraction

Five ml of blood was collected in EDTA vials and DNA was extracted from blood lymphocytes using 'salting out' method (Miller et al., 1998).
population were compared using χ² test (Tables 2, 3 and 4). The minor allele frequency in our population was 27%, 25% and 28% for OGG1 Exon 7, XPC PAT and XPC Exon 15 respectively. In case of OGG1 Exon 7 (C1245G) significant frequency distribution was observed in Japan, Spain, Norway and Korea as compared to our population. Significantly different pattern of genotype and allele frequencies was reported in XPC PAT polymorphism in USA, Spain and Canada population. Genotype and allele distribution of XPC Exon 15 (A33512C) polymorphism was significantly different from Texas, Minnesota and USA.

### Discussion

Functional polymorphisms of genes for DNA repair are of particular importance from the point of view that they are implicated in the pathogenesis of complex genetic disorders. A number of studies suggest that such mild defects in DNA repair may predispose to cancer (Au et al., 2004). Due to marked differences in the distribution of DNA repair polymorphisms, between various worldwide ethnic groups, the data from 'normal healthy' populations are of special interest for finding out the relevance as well as the evaluation of the investigated genetic markers in susceptibility, manifestation, prognosis or treatment of diseases. It is well recognized that ethnic background may influence the susceptibility to suffer from certain diseases (Kittles et al., 2003). Therefore, variation in our Indian population in contrast to other populations worldwide signifies the impact of ethnicity. Indian population is believed to be most diverse because of different socio-cultural traditions. The study of genetic variation can elucidate critical determinants in environmental exposure and cancer, which could have future implications for preventive and early intervention strategies. The differences in the allelic frequencies detected among these studies might be due to several reasons such as ethnic variation, heterogeneity of study populations and different sample sizes.

In OGG1 Exon 7 (C1245G) polymorphism, the (G*) allele frequency in Indian population was 27%, which was significantly higher in Japan, Spain, Norway, Korea and Turkey and no significant difference was observed from Minnesota, USA and Polish. The (I*) allele frequency in XPC PAT polymorphism was 25% in our population. This was significantly lower as compared with that of USA, Spain and Canada. In XPC Exon 15 (A33512C) polymorphism, the (C*) allele frequency in Indian population was 28.1% which was significantly higher as compared to observations from populations in Texas, Minnesota and USA.

In a study from Minnesota and Turkey by McWilliams et al., 2008, and Karahalil et al., 2008, the minor variant allele frequencies were found to be almost similar with our northern population for OGG1 Exon 7 (27% vs. 24.8% and 32.8%) respectively.

Although the increased/decreased risk associated with individual DNA repair SNPs may be small compared to that conferred by high-penetrance cancer genes, their public health implication may be large because of their high frequency in the general population. Epidemiological investigations of DNA repair polymorphisms are therefore important (Wacholder et al., 2004). Large and combined analyses may be preferred to minimize the likelihood of both false-positive and false-negative results. Appropriate, confounding factors should be controlled, in particular consideration of race and ethnicity. As there are differences in the prevalence of DNA repair polymorphisms across different populations, hence, it is important to keep in mind that a susceptibility factor in one population may not hold true for another. Such kind of study may form the basis for future establishment of epidemiological and clinical databases. The present analyses suggest that OGG1 and XPC polymorphisms may be biomarkers of disease susceptibility and may be contributing factors in the risk of cancer development. A single larger study with thousands of subjects and tissue-specific biochemical and biological characterization is warranted to further evaluate potential gene-to-gene and gene-to-environment interactions on DNA repair polymorphisms and cancer risk. The differences in these genes distribution between North Indian healthy population and other ethnic groups may help in building a profile that would help in assessing the disease predisposition and prevalence.
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References


